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BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

**Re: Docket No. 02P-0406
Comments to Suitability Petition**

Dear Sir or Madam:

We are writing on behalf of GlaxoSmithKline (GSK) regarding the above-referenced suitability petition, submitted by The Weinberg Group on September 10, 2002. This petition seeks a determination that amoxicillin/clavulanate potassium 600 mg/42.9 mg tablets for oral suspension are suitable for submission in an abbreviated new drug application (ANDA). The reference product cited in the petition is GSK's Augmentin ES-600® powder for oral suspension.

According to the Food and Drug Administration (FDA), if the change proposed in a suitability petition does not qualify for a full waiver of pediatric studies under the Pediatric Research Equity Act (PREA), that petition will be denied, because clinical studies will be required to demonstrate the safety and/or effectiveness of the change. For the reasons stated below, The Weinberg Group's suitability petition fails to qualify for such a waiver.

Furthermore, recent developments, including FDA's denial of a closely related suitability petition, confirm that The Weinberg Group's tablets for oral suspension cannot be dosed in the precise increments offered by GSK's powder for oral suspension. For this reason as well, The Weinberg Group's suitability petition must be denied, because it raises significant questions of safety and effectiveness.

02P-0406

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I. BACKGROUND

On September 10, 2002, The Weinberg Group submitted to FDA a suitability petition, seeking a determination that amoxicillin/clavulanate potassium 200 mg/28.5 mg, 400 mg/57 mg, and 600 mg/42.9 mg tablets for oral suspension are suitable for submission in ANDAs. *See* Docket No. 02P-0406 (the 2002 Petition); *see also* 21 USC 355(j)(2)(C); 21 CFR 314.93. The reference listed drugs (RLDs) cited in the petition were Augmentin® and Augmentin ES-600® powder for oral suspension.

On December 19, 2002, GSK submitted comments in opposition to this petition. GSK noted that in addition to a change in dosage form, The Weinberg Group also sought a change in the approved dosing regimen, because tablets for oral suspension cannot be dosed in the precise, mg/kg increments offered by GSK's powder for oral suspension.¹ As explained in GSK's comments, besides being impermissible under a suitability petition, The Weinberg Group's proposed change would require clinical study and substantial re-labeling of the reference products.

The Weinberg Group replied to GSK's comments on May 16, 2003, and submitted additional comments on November 19, 2003. In the latter comments, The Weinberg Group reported that FDA had indicated the proposed 200 mg/28.5 mg and 400 mg/57 mg tablets for oral suspension may be suitable for submission in an ANDA, if the RLD were changed to Augmentin® chewable tablets. On January 30, 2004, GSK replied to this submission, supporting FDA's apparent decision to deny The Weinberg Group's petition, insofar as it sought permission to submit ANDAs referencing GSK's powder for oral suspension products.

Shortly thereafter, FDA issued a letter to The Weinberg Group, stating that review of its petition could not continue, unless required pediatric studies were waived. According to FDA, the recently-enacted PREA requires that all applications for new active ingredients, indications, dosage forms, or routes of administration include assessments of the safety and effectiveness of the products in all relevant pediatric populations. *See* Letter from G. Buehler to N. Fleischer, Ph.D., Docket No. 02P-0406 (Feb. 3, 2004) (PREA Letter); *see also* Pub. L. No. 108-155, 117 Stat. 1936 (2003) (codified at 21 USC 355c).

¹ For example, GSK demonstrated that a 20 kg pediatric patient, who would receive 900 mg of amoxicillin in 7.5 mL of Augmentin ES-600® twice daily, would receive either 600 or 1200 mg of amoxicillin from one or two tablets for oral suspension twice daily, along with a different dose of clavulanate potassium. *See* Comments to Petition, Docket No. 02P-0406 (Dec. 19, 2002) at 4, 7.

Division of Dockets Management
June 28, 2004
Page 3

FDA informed The Weinberg Group that its suitability petition is subject to this requirement. "If the change proposed in an ANDA suitability petition does not qualify for a full waiver of the pediatric studies," the agency wrote, "that petition will be denied because, under PREA, clinical studies are required to demonstrate the safety and or effectiveness of the change" PREA Letter.²

In response, The Weinberg Group submitted to FDA a request for a full waiver of pediatric studies. *See* Amendment to Petition, Docket No. 02P-0406 (Mar. 10, 2004) (Pediatric Waiver Request). The Weinberg Group argued that its proposed products do not represent a meaningful therapeutic benefit for, and would not likely be used in a substantial number of, pediatric patients. *See id.*; *see also* 21 USC 355c(a)(4)(A)(iii).

Finally, on April 1, 2004, The Weinberg Group withdrew from the 2002 Petition its request for a determination that amoxicillin/clavulanate potassium 200 mg/28.5 mg and 400 mg/57 mg tablets for oral suspension are suitable for submission in an ANDA. Rather, The Weinberg Group submitted a new petition for this product, citing Augmentin® chewable tablets as the RLD. *See* Docket No. 04P-0157 (Apr. 1, 2004). Included in this new suitability petition is a second request for a full waiver of required pediatric studies. The Weinberg Group's earlier suitability petition, concerning 600 mg/42.9 mg tablets for oral suspension, remains pending.

II. ARGUMENT

A. The Weinberg Group's Suitability Petition Does Not Qualify for a Full Waiver Under the Pediatric Research Equity Act

Under the Pediatric Research Equity Act, FDA may grant a full waiver of required pediatric studies if a drug: "(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; *and* (II) is not

² FDA's application of the PREA to suitability petitions is consistent with its practice under its invalidated "Pediatric Rule." *See* 63 FR 66632, 66641 (Dec. 2, 1998) ("FDA notes that petitions submitted under section 505(j)(2)(C) . . . may be denied if 'investigations must be conducted to show the safety and effectiveness of the change.'"); Draft Guidance for Industry: *Recommendations for Complying with the Pediatric Rule (21 CFR 314.55(a) and 601.27(a))* 3 (Nov. 2000) ("Applications for drugs that are not duplicates of already approved products are required to comply with the rule. This includes applications submitted under 505(j)(2)(C) suitability petitions . . .").

likely to be used in a substantial number of pediatric patients.” 21 USC 355c(a)(4)(A)(iii) (emphasis added). Because The Weinberg Group’s suitability petition does not qualify for a waiver under this standard, it must be denied; clearly, clinical studies will be needed to demonstrate the safety and/or effectiveness of the change. See PREA Letter.³

1. *The Benefit from The Weinberg Group’s Proposed Product Is Directed to the Pediatric Population*

In its first waiver request, The Weinberg Group claimed that its products provide “a more convenient dosage form” with respect to unit-dose dispensing, ease of administration to patients who have difficulty swallowing, and storage. Pediatric Waiver Request at 2.⁴ Nevertheless, The Weinberg Group stated that its products do not represent a meaningful therapeutic benefit for pediatric patients, because these benefits, “while not excluding pediatrics, are directed to the adult population.” *Id.*

GSK disagrees with the assertion that the potential benefits of the tablet for oral suspension dosage form “are directed to the adult population.” Augmentin ES-600® is approved for use *only* in children with recurrent or persistent acute otitis media (AOM), so any benefit from an alternate version *must* be directed to the pediatric population. See Augmentin ES-600® Labeling, *Indications* (2004) (attached at Tab 1). Also, children often are unable or unwilling to swallow tablets or capsules, which can lead to compliance concerns and sub-therapeutic dosing. Ranbaxy Pharmaceuticals cited increasing compliance in such children as a primary reason for its development of DisperMox™ (amoxicillin) 600 mg tablets for oral suspension. See Press Release (Dec. 8, 2003) (attached at Tab 2). Clearly, the The Weinberg Group’s proposed product is directed to pediatric patients.

³ The PREA also provides for a full waiver of pediatric studies if such studies are impossible or highly impracticable, or if there is evidence strongly suggesting that the drug would be ineffective or unsafe in all pediatric populations. See 21 USC 355c(a)(4)(A). The Weinberg Group does not argue that its suitability petition qualifies for a waiver under either of these standards.

⁴ As discussed below and in GSK’s prior submissions to Docket No. 02P-0406, The Weinberg Group’s tablets for oral suspension do not offer more convenient, unit-dose dispensing, but rather are dosed according to a different dosing regimen than Augmentin ES-600®. Also, they are not easier to administer to patients who have difficulty swallowing, because both the proposed and reference products are administered to the patient in the form of a suspension. See Comments to Petition, Docket No. 02P-0406 (Jan. 30, 2004 & Dec. 19, 2002).

2. *The Weinberg Group's Proposed Product is Likely to be Used in a Substantial Number of Pediatric Patients*

In its first waiver request, the Weinberg Group acknowledged that its proposed products would be approved for use in pediatric patients, 3 months of age and older, within the correct weight range for dosing. "Based on the limited pediatric patient population," however, The Weinberg Group claimed that "there will not be substantial use of the product in pediatric patients, and therefore does not warrant a pediatric study." Pediatric Waiver Request at 5.

The assertion that The Weinberg Group's proposed product will not be used in a substantial number of pediatric patients is implausible. As noted above, Augmentin ES-600® is approved for use *only* in children with recurrent or persistent AOM. See Tab 1. Moreover, Ranbaxy's press release announcing the approval of amoxicillin 600 mg tablets for oral suspension states that AOM is the most common cause of pediatric office visits in the United States, exceeding 35 million in 2001. See Tab 2.

In fact, an adult dose of Augmentin ES-600® would exceed the maximum FDA-approved dose of amoxicillin. Augmentin ES-600® is dosed at 90 mg/kg/day (by amoxicillin). See Tab 1. A 70 kg adult therefore would receive 6300 mg per day, while the maximum approved daily dose of amoxicillin is 4000 mg per day. See Augmentin XR™ Labeling, *Dosage and Administration* (2004) (attached at Tab 3). For this reason, the labeling of Augmentin ES-600® contains the statement, "[e]xperience with AUGMENTIN ES-600 (600 mg/5 mL formulation) in adults is not available and adults who have difficulty swallowing should not be given AUGMENTIN ES-600 (600 mg/5 mL) in place of the 500-mg or 875-mg tablet of AUGMENTIN." Tab 1.

* * *

The Weinberg Group acknowledged in its request for a waiver of pediatric studies that, under the PREA, it must be shown that the drug does not represent a meaningful therapeutic benefit over existing therapies *and* is not likely to be used in a substantial number of pediatric patients. The Weinberg Group's request, however, plainly fails to meet these requirements. As recognized by FDA, this mandates denial of the suitability petition itself, because clinical studies will be required to demonstrate the safety and/or effectiveness of the proposed change.

B. The Weinberg Group's Suitability Petition Raises Questions of Safety and Effectiveness

Several recent developments confirm – as GSK argued in its original comments – that The Weinberg Group's suitability petition raises significant questions of safety and effectiveness. First, FDA recently denied a suitability petition in which The Weinberg Group sought permission to submit an ANDA for a closely related product. One of FDA's grounds for denying this petition is directly applicable to this proceeding. Second, in its request for a waiver from pediatric studies, The Weinberg Group confirms that its proposed product cannot be dosed according to the approved, Augmentin ES-600® dosing regimen.

1. The Agency Recently Denied a Closely Related Tablet for Oral Suspension Suitability Petition

On April 29, 2004, FDA denied a suitability petition, submitted by The Weinberg Group, which sought a determination that cefuroxime axetil 125 and 250 mg tablets for oral suspension were suitable for submission in an ANDA. See Docket No. 02P-0414 (attached at Tab 4). The RLD cited in the petition was GSK's Ceftin® powder for oral suspension.

In denying this petition, the agency concluded that The Weinberg Group's proposed change raised questions of safety and/or effectiveness, and that clinical trials would be required for the product. The first of the reasons FDA gave for denying the petition is directly applicable to The Weinberg Group's current petition regarding Augmentin ES-600®, and merits quoting at length:

The labeling for the listed drug provides that dosing for pediatric patients is calculated based upon the patient's weight (mg/kg) and the specific infection being treated. The labeling for the listed drug also provides specific amounts of water (in mLs) that are required to be administered for reconstitution of the product. By contrast, although your petition proposes dosing for pediatric patients calculated based upon the patients' weight (mg/kg) and the specific infection being treated, it does not provide for a specific amount of water to be administered for the dosage. Recommendations for administering your proposed product state that the tablet for oral suspension needs to be dissolved in one tablespoonful (15 mLs) to two ounces (60 mLs) of

water. These figures range from less than half to greater than 50% more than the specific amount of water that the listed drug labeling recommends. Because your proposed product lacks a standard required numerical amount of diluent, unlike the listed drug, those administering the drug as directed will do so with varying concentrations of the product and without reference to the specific amount recommended for the listed drug. As a result, end concentrations of the product as presented for ingestion will vary among users and potentially even by the same user on different occasions. FDA has determined that for drugs dosed on a per weight (mg/kg) basis, the lack of a standardized end concentration poses safety concerns with regard to over/under dosing.

Id.

Precisely the same reasoning applies to Augmentin ES-600[®]. Like Ceftin[®], Augmentin ES-600[®] is dosed according to the weight of the patient, at 90 mg/kg/day, divided every 12 hours. *See* Tab 1. And, like Ceftin[®], the labeling of Augmentin ES-600[®] provides specific amounts of water for reconstitution of the product. For bottle sizes of 50, 75, 100, and 150 mLs, the labeling instructs providers to use 45, 65, 90, and 130 mLs of water, respectively. *See id.*

By contrast, just as with its cefuroxime axetil product, the proposed labeling of The Weinberg Group's amoxicillin/clavulanate potassium tablets for oral suspension does not provide for any specific amount of water for reconstitution. Rather, it relies on the identical "1 tablespoonful to 2 ounces of water" language found deficient by FDA. *See* Tab 4; *see also* 2002 Petition at 11. Thus, the end concentration of the proposed product will differ significantly from that of Augmentin ES-600[®], and even from the concentrations of different preparations of the product itself. As recognized by FDA, this poses serious safety concerns, which require denial of The Weinberg Group's petition.⁵

⁵ The Weinberg Group recently petitioned FDA to reconsider its denial of the Ceftin[®] suitability petition. *See* Petition for Reconsideration, Docket No. 02P-0414 (June 1, 2004). In its petition, The Weinberg Group proposes to specify an amount of water to be used for reconstitution. *See id.* at 2. The Weinberg Group has not made such a proposal in this proceeding; to do so it would need to amend its suitability petition to allow for comment. Moreover, it is unlikely that The Weinberg Group could, by specifying an amount of diluent, replicate the weight-based dosing schedule for amoxicillin/clavulanate potassium 600 mg/42.9 mg powder for oral suspension. Among other things, even if a fixed concentration of suspension could be achieved by specifying an amount of

GSK raised this precise issue in our previous comments in opposition to The Weinberg Group's petition. *See* Comments to Petition, Docket No. 02P-0406 (Dec. 19, 2002). In our original comments to the docket, we noted that, based on weight per volume, the strength of the proposed product is markedly different from that of the reference product. For example, Augmentin ES-600® contains 120 mg of amoxicillin per 1 mL of suspension. The strength of the proposed product varies, depending on whether it is suspended in 1 tablespoon to 2 ounces of water, but in all cases is more dilute than the reference product. *See id.* at 7-8. We also warned that nowhere in the proposed labeling are there instructions on whether or how to dose the product according to the approved, Augmentin ES-600® dosing regimen. As a result, depending on how a caregiver attempts to compensate for this problem, a child may end up over/under dosed. *See id.*

Based on these comments, and on the agency's own reasoning in its recent denial of the Ceftin® suitability petition, it is clear that The Weinberg Group's current petition presents serious safety concerns regarding the potential for improper dosing. FDA should therefore deny this petition, and any future petitions for products incapable of replicating the precise, mg/kg dosing afforded by a powder for oral suspension.

2. *The Weinberg Group's Waiver Request Confirms that its Product Cannot be Dosed According to the Approved Dosing Regimen*

Finally, in its first request for a waiver from required pediatric studies, The Weinberg Group provided additional information on the dosing of its proposed 600 mg/42.9 mg tablets for oral suspension. *See* Pediatric Waiver Request at 4. This information confirms that the product cannot be dosed according to the approved, Augmentin ES-600® dosing regimen.

The approved dose of Augmentin ES-600® is 90 mg/kg/day, divided every 12 hours. *See* Tab 1. As described above, GSK's powder for oral suspension dosage form allows the dose to be calibrated to the weight of the patient, in 180 mg increments (by amoxicillin). To ensure accurate calculation of the dose, the labeling

diluent, additional labeling would be needed to instruct the patient on how much of the suspension to swallow. This, however, is counter to the concept of the tablet for oral suspension dosage form, in which the patient is supposed to simply "swirl and swallow" the entire suspension.

of Augmentin ES-600® includes a table with the proper doses for patients weighing 8, 12, 16, 20, 24, 28, 32, and 36 kg. *See id.*

By contrast, The Weinberg Group's waiver request makes clear that its proposed product can only be dosed in 600 mg increments (by amoxicillin). The request includes The Weinberg Group's version of GSK's dosing table, and recommends one or two 600 mg/42.9 mg tablets for oral suspension every 12 hours, for patients weighing 13 or 26 kg, respectively. *See Pediatric Waiver Request at 4.* No other guidance is given and, consistent with the dosing of Augmentin ES-600®, patients of different weights should not be prescribed the product. To our knowledge, FDA has never approved a generic drug for use in such a small and discontinuous subset of a reference drug's target population.

Rather, The Weinberg Group clearly intends for its product to be dosed according to a different dosing regimen than that approved for Augmentin ES-600®. Under this dosing regimen, one or two tablets for oral suspension would be prescribed to patients of widely varying weights. As GSK has noted previously, this change in the approved dosing regimen would require additional clinical study and substantial re-labeling of the reference product. *See Comments to Petition, Docket No. 02P-0406 (Jan. 30, 2004 & Dec. 19, 2002).*

Moreover, such a change to an approved product's dosing regimen is impermissible under a suitability petition. *See* 21 CFR 314.93(a) ("Petitions to submit abbreviated new drug applications for other changes from a listed drug will not be approved."); *see also* Letters from G. Buehler, Docket Nos. 01P-0130 & 01P-0283 (July 9 & 3, 2002) (denying petitions and stating that "a change in dosing regimen is not petitionable under Section 505(j)(2)(C) of the Act.").

III. CONCLUSION

The Weinberg Group's suitability petition raises the fundamental issue that a tablet for oral suspension simply cannot match the approved dosing regimen of a powder for oral suspension, or of any other product dosed on a mg/kg basis. The agency recognized this in its recent denial of The Weinberg Group's suitability petition concerning cefuroxime axetil tablets for oral suspension.

Now, through its submission of a request for a waiver from required pediatric studies, The Weinberg Group has demonstrated another reason why its suitability petition must be denied. Because this petition does not meet the

HOGAN & HARTSON L.L.P.

Division of Dockets Management

June 28, 2004

Page 10

requirements for a full waiver under the Pediatric Research Equity Act, clinical studies will be required to demonstrate the safety and/or effectiveness of the change. The petition therefore must be denied.

Sincerely,



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Attachments

cc: Gary Buehler, Director, Office of Generic Drugs, HFD-600
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